

Current status of cacanakinumab therapy for cardiovascular disease

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Abstract. Cardiovascular disease(CVD)is an important cause of death in the worldIn recent years, due to a large number of experimental results, people gradually abandon the previous view the CVD is caused by hyperlipidemia, and the CVD is caused by a chronic, low-intensity inflammatory response in blood vessels. in which inflammation is thought to be a key facilitator.However, there are limits to the study of drugs that use CVD for excessive inflammation.The Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial, conducted in 2017, successfully demonstrated that inflammation plays an important role in atherosclerotic disease. Canakinumab is an antibody that can effectively inhibit the activation of IL-1 beta. The results of the Cantos trial ushered in a new era of new treatments aimed at treating cardiovascular diseases.Although the targeted anti-AS effect of CANTOS is prominent, its efficacy does not significantly improve the mortality and infection rate of patients with cardiovascular disease.To this end, we collected relevant data of Carnaro umab in recent years. This paper will focus on its clinical application and analyze its advantages and disadvantages, and give the possible improvement and development direction.

Keywords: Canakinumab, atherosclerotic, inflammation.

1. Introduction

Cardiovascular disease is also known as a disease of blood circulation in clinic. The circulatory system is made up of the heart and blood vessels. It is the organ and tissue that carries blood in the human body. Cardiovascular diseases can be subdivided into acute cardiovascular diseases and chronic cardiovascular diseases [1]. The most common cardiovascular diseases are essential hypertension and coronary atherosclerotic heart disease (coronary heart disease).Although smoking, hypertension, diabetes and other common cardiovascular diseases have been effectively prevented and treated, many people still suffer from serious cardiovascular diseases, of which about 40% of people with normal blood lipids die of myocardial infarction [2]. Studies have shown that the pathogenesis of AS is not only related to dyslipidemia, but also closely related to inflammation. Recently, a large number of experiments have confirmed this idea.

The commonly used drugs for thetreatment and prevention of cardiovascular diseases are interventional therapy and anticoagulation therapy for the purpose of controlling risk factors, but the targeting of inflammatory response has not been reported. Recently, Canakinumab (CANTOS) can significantly reduce residual inflammatory response and mortality without affecting the level of LDL. In contrast, the use of the broad-spectrum anti-inflammatory drug MTX does not reduce the risk and mortality of cardiovascular disease [3]. So,It is of great significance to find new therapeutic targets and inhibit the occurrence and development of AS.Interleukin-1 β is a cytokine that is central to the inflammatory, Canazinzumab as an antagonist targeting IL-1 β , is a fully humanized monoclonal antibody targeting interleukin 1 β with high affinity. Canazinzumab works by consistently blocking IL-1 β , thereby inhibiting inflammation caused by its overproduction. Canazinzumab can inhibit the production of autoinflammatory response.

However, Canakinumab's market performance has been flat for nearly ten years since its launch. From 2009 to 2016, the annual sales of Canakinumab increased by only tens of millions of dollars [4], which does not fit the profile of a blockbuster drug. This may have something to do with canakinumab's high price, safety concerns and poor results.

Based on the current status of canakinumab in cardiovascular therapy, this review focuses on analyzing the advantages and limitations of canakinumab from the perspective of disease and treatment principles, and give some suggestions and hopes.

2. The hypothesis of atherosclerosis pathogenesis

The pathogenesis of atherosclerosis has been studied for more than a century, with various theories surrounding the theory of fat infiltration, platelet aggregation and thrombosis, injury response and inflammation. As early as the end of last century, two scientists proposed the inflammatory hypothesis of atherosclerosis. Early large-scale cohort studies found that the level of serum inflammatory markers could independently predict the first occurrence and recurrence of adverse cardiovascular events, and subsequent studies successively found a series of inflammatory factors related to atherosclerosis. In some basic experiments, the mechanism of some inflammatory factors participating in the arteriosclerosis process has been confirmed. So inflammation has long been thought to play a key role in the process of atherosclerosis (Fig 1). Unfortunately, there are currently no "anti-inflammatory" drugs in the strict sense of the term used directly for the treatment of atherosclerosis. The CANTOS study published in 2017 first directly demonstrated the Canakinumab can reduce the incidence rate of cardiovascular disease, which has epoch-making significance [5].

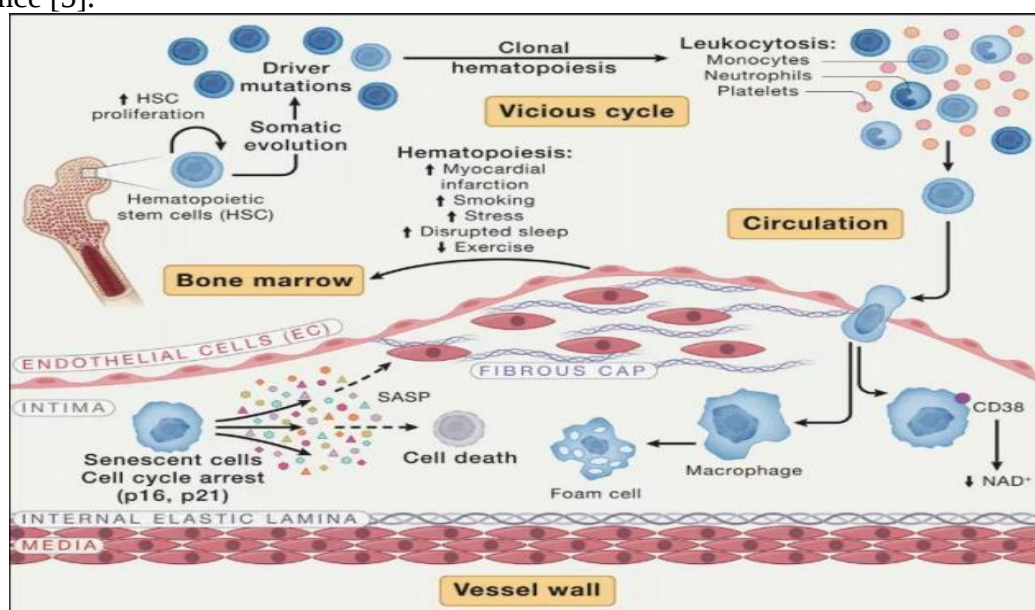


Fig. 1 Schematic diagram of cardiovascular disease [5].

3. Mechanism of Action and Indications

IL-1 is a kind of inflammatory factor with pro-inflammatory effect. Interleukin-1 (IL-1) is an important molecule that interleukin-1 (IL-1) regulates the expression of interleukin-1. IL-1 β is a kind of important cytokines, which are mainly derived from macrophages, keratinocytes, fibroblasts and so on. IL-1 β is mainly formed by a plasma polypeptide (Pro-IL-1 β) and released into the inflammatory body complex after cleavage by Caspase-1. IL-1 R II is the main effector molecule of IL-1 (IL-1 β)-1 receptor (IL-1 R II).

As a ubiquitous cytokine, interleukin-1 β (IL-1 β) can regulate IL-6 signal pathway and promote inflammatory response. Almost all nucleated cells can synthesize IL-1 β , which mainly comes from activated mononuclear macrophages and lymphocytes. These two kinds of cells are the "sentinel cells" of biological innate immune system, which can timely alert the abnormal metabolic activities in the biological body [6].

3.1. Production and regulation of IL-1 β

The release of IL-1 β involves three key steps, the first step is the production of proto-IL-1 β with weak biological activity; and the second step is aspartase-1 lysate proto-IL-1 β to produce mature, bioactive IL-1 β , in the end, Secretion of mature IL-1 β into the extracellular environment (Fig 2).

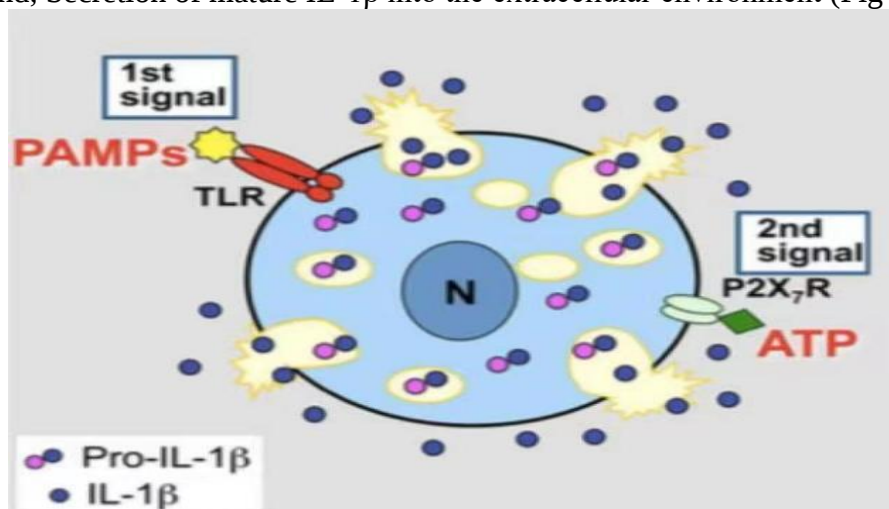


Fig. 2 Production process of IL-1 β [6].

3.2. Signal transduction of IL-1 β

Signal transduction of IL-1 β is mainly mediated by the IL-1 β receptor-associated kinase pathway (IPAK pathway). Firstly, IL-1 β induces conformational change in the extracellular region of IL-1RI, recruits IL-1RAcP, forms a trimer complex of IL-1 β /IL-1RI/IL-1RAcP, and then activates protein kinase 4 (IPAK4) and bone marrow differentiation factor-88 (MyD88 [7]). At the same time, IL-1R activates self-phosphorylation of protein kinase 4, phosphorylation of IPAK1 and IPAK2, followed by recruitment of oligonucleated tumor necrosis factor receptor-associated factor (TRAF6), which activates the mitogen bound protein kinase MAPKKK family. Activation of NIK, 1KK, 1KB phosphorylation and degradation of 1kB, and transfer of uninhibited NF- κ B into the nucleus to regulate expression of related genes. The signal transduction pathway of IL-1 β can also activate other pathways through various bridging factors, for instance MAPKs ,NF- κ B, activating protein-1 (AP-1), c-Jun amino acid kinase (JNK), phosphatidylinositol 3 (PI3) and other signaling pathways .

There are multiple pathways to IL-1-induced inflammatory processes, but its two main subunits, IL-1 α and IL-1 β , are currently the most studied directions. The induction process is as follows: the first step is to connect IL-1 α or IL-1 beta to an IL-1-R1 respectively. On this basis, the complexes composed were used to recruit aptamers. which then recruits an adaptor protein. Covering the IL-1 β -binding site of Canakinumab. Canakinumab heavy and light strand complementary DNA was cloned by Assembly PCR. Studies have shown that pre-Canakinumab can be specifically activated in the area of self-inflammation, thus increasing the sensitivity to self-inflammation.

4. The clinical trials of Canakinumab in CVD

Novartis released the results of the CANTOS clinical trial in June 2017 and found that Canabumab reduced the number of patients with coronary heart disease and inflammatory plaques with inflammatory plaques by 15% compared with the statin placebo group. Novartis released a study on the third phase of CANTOS in November 2017, in which patients began using Canakinumab for 3 months, for those patients with a history of heart attack who had a high sensitivity C-reactive protein (hsCRP) drop below 0.002g/L, major cardiovascular adverse events (MACE) were reduced by a quarter (compared with placebo. In addition, these patients had a significant reduction 31% in cardiovascular (CV) mortality and all-cause mortality (The largest cardiovascular clinical trial ever conducted by Novartis has demonstrated the significant efficacy of canakinumab in the treatment of

inflammatory atherosclerotic diseases and will provide new treatment options for patients with inflammatory atherosclerosis worldwide [8].

In November 2017, Novartis announced further analysis results from the CANTOS Phase III clinical trial, demonstrating that canakinumab is significant in the treatment of inflammatory atherosclerotic disease and will provide new treatment options for patients with inflammatory atherosclerosis worldwide.

An analysis of secondary clinical trials of patients with adverse cardiovascular events showed that Canakinumab use was associated with a positive risk of adverse cardiovascular events in patients with chronic kidney disease when compared with placebo.

A clinical study of Novartis Cantos shows that canacol umab reduces the risk of heart disease in diabetic patients by 10% compared with placebo, The purpose of this study was to investigate whether kanesuzumab can delay or prevent the development of prediabetes and reduce the risk of heart disease in patients. People with pre-diabetes had a 14 percent lower risk [9].

5. Advantages of canakinumab in the treatment of cardiovascular diseases

A key advantage is its high specificity, reducing the risk of off-target toxicity common in small molecule agents, which is particularly important for treating rare diseases, which often require long-term drug management.

Another advantage of canakinumab is based on its high specificity, is its stability in vivo, thus allowing for long-spaced dosing regimens (e.g., once a month).

For rare diseases caused by circulation and/or "functional gain" of specific proteins on the cell surface, the corresponding MAB therapy technology is relatively mature.

Moreover, new technologies such as phage display are becoming more and more accessible. Canakinumab is a kind of human antibody with the activity of inhibiting IL-1 β , which is obviously different from other drugs such as Anakinra and Rilonacept. Canakinumab is administered once a month for 150-300 mg (2-4 mg/kg for children) [10]. It can be used for the prevention and treatment of CAPS, Tumor necrosis factor receptor cycle syndrome, hyperimmunoglobulin D syndrome, and systemic arthritis in children. A preliminary study of phase II in the CANTOS clinical trial 185 showed that 1.5 mg/kg of Canarom alone was enough to reduce CRP by more than 40% within 12 weeks.

6. Clinical status of canakinumab

To date, most clinical studies of canakinumab have focused on cap and three types of arthritis [rheumatoid arthritis (RA), general-onset juvenile idiopathic arthritis (SoJIA) and gouty arthritis]. The drug is also used to treat COPD, diabetes and age-related retinal degeneration [11].

Canakinumab may cause serious infections, especially upper respiratory tract infections, because interleukin-1 blocking may interfere with the immune response to infection. In the CANTOS trial, patients receiving Canakinumab had nearly twice as many severe infections and sepsis as those receiving a placebo. However, death from infection was not significantly different between the Canakinumab and placebo groups, and the deaths were mostly elderly patients with diabetes. Some scientists suggests that interleukin-1 β is driven by multiple inflammatores and precisely inhibits a single one, Such as NLRP3 (pyrin domain-containing protein 3, NOD-like receptor family) will be more promising. If NLRP3 is selectively suppressed, leaving the opportunity for other inflammasome to fight infection, clinical application will be safer. Because unlike oral drugs, which can be withdrawn at the first sign of a serious infection, Canakinumab cannot .Canakinumab is injected subcutaneously and has a half-life of up to 26 days in vivo [12].

Since its first approval in 2009, canakinumab has been approved for rare autoinflammatory diseases, refer to a good deal terrivory. including: Cryptosis-related menstrual cycle syndrome,

systemic childhood specific arthritis (SJIA), TRIPS, HIDs/MKD, familial Mediterranean fever (FMF) and other fields.

7. Limitations and Future direction

7.1. Limitations

7.1.1 Safe

As an immunosuppressant, Canakinumab's safety has been proved to a large extent in the past 10 years of studies. In the study results published by Novartis, the main adverse effect of Canakinumab is similar to that of other immunosuppressants, that is, it increases the risk of serious infection in patients. No serious toxicity or increased all-cause mortality was found in other organs [13].

However, canakinumab may cause side effects. Physical symptoms such as hives, rashes, itching, difficulty breathing or swallowing, dizziness, fainting, rapid or irregular heartbeat. canakinumab may increase the risk of some types of cancer when taken over a long period of time. Increased risk of lymphoma and may weaken defenses against malignant tumors.

7.1.2 Therapeutic effect

Compared with small molecules, the "large size" of monoclonal antibodies limits their tissue and cell penetration, preventing them from reaching some theoretically desirable targets, monoclonal antibodies need to be injected (and therefore require a very high standard of sterility when formulated) and can trigger adverse reactions at the injection site -This is the same problem with other macromolecular drugs such as protein replacement therapy.

7.1.3 High cost

Among the drawbacks of Canakinumab so far is its high price tag, In the CANTOS study, the annual cost of Canakinuma was approximately 60 thousand. Its current selling price is about 0.2g/19800 yuan, which is expensive. This will result in some patients who really need it being unable to use it due to its high price and timely treatment [14].

7.2. Future directios

While the current accessibility of mab technology is far from adequate, it is expected to improve in the future based on two major technological developments.

Efficient and safe identification and preparation of monoclonal antibodies are also developing. Higher antibodies can be obtained by batch, feeding batch and continuous perfusion, which significantly reduces the cost of antibody preparation and improves the flexibility of antibody preparation.

IL-1 β is a new target, and more and more drugs based on this target will be developed in the future, possibly leading to more powerful classes. Flame Biosciences, for its part, raised \$100 million in funding in October 2020[15]. The fledgling company, which is also focusing on IL-1 β , thinks its drug is ten times more effective than Canakinumab.

The entry into the market of affordable biosimilar mab is expected to promote the redevelopment of MAB [16]. For example, in a large number of sequencing data such as Genome Programming in the UK, for patients with rare diseases who are currently lack of effective treatment, the efficacy mechanism of high-quality antibodies can be compared with the pathogenesis of rare diseases, to reach patients with rare diseases who currently lack treatment options [17].

8. Conclusion

Statins, Kupffer-9 inhibitors and precise vascular remodeling have been used, but the risk of recurrence is still high. CANTOS test will lay a foundation for the study of the pathogenesis and clinical application of CVD. Canakinumab could effectively inhibit IL-1 β , IL-6 and high sensitivity

reactive protein, but had no significant effect on LDL, suggesting that Canakinumab may play a role by inhibiting IL-1 β and IL-6. Canakinumab is currently the only anti-inflammatory drug that can reduce cardiovascular disease caused by inflammatory indicators without affecting cholesterol in the body. The risk of both primary and secondary endpoints outcomes was significantly reduced in the kanaxine group, but no reduction in systemic or cardiovascular mortality was found in the CANTOS group. In addition, side effects of canakinumab treatment included a decrease in white blood cells and a higher rate of fatal infection. It has not been used in clinic because of its high cost and serious side effects. We hope that in the future, by improving the target, increasing the efficacy of canakinumab or expanding the range of action and reducing the cost, canakinumab will be able to better treat related diseases and enable more and more patients to get rid of the disease. In recent years, with the deepening of immunological research, we have a new understanding of the pathogenesis of cardiovascular disease. This study will provide a new theoretical basis for the prevention and treatment of coronary heart disease. It will be a painstaking and valuable process.

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